Ximelagatran (Exanta): alternative to warfarin?

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For decades, the standards of antithrombotic therapy have been heparin and coumarin compounds, primarily warfarin (1). Other newer approaches include low-molecular-weight heparins, fondaparinux, lepirudin, argatroban, and melagatran (investigational). Although existing treatments are effective, they have many limitations. A safer, more convenient therapy is needed. Ximelagatran is the first oral treatment in a new World Health Organization class of direct thrombin inhibitors and is the first new oral anticoagulant since the introduction of warfarin almost 60 years ago (2). It was submitted to the Food and Drug Administration (FDA) for approval in December 2003 (3).

Each year, nearly 4 million people worldwide experience a primary thrombotic event, and those at greatest risk include people with atrial fibrillation, those who have experienced a previous cardiac event such as a myocardial infarction, and patients who have recently undergone orthopaedic surgery, such as total hip or knee replacement surgery (4). Current mainstays of therapy for preventing or treating thrombosis are not ideal. Warfarin, although available in an oral form, has a slow onset of action, interacts with numerous foods and drugs, and requires intensive monitoring of coagulation with frequent dose adjustments. Heparins, fondaparinux, lepirudin, argatroban, and melagatran (investigational) are limited by their route of administration, especially in an outpatient setting, as all are administered parenterally (5, 6). Ximelagatran, a prodrug of melagatran, is an orally administered direct inhibitor of both free and clot-bound thrombin. It is rapidly absorbed and quickly converted to its active form, melagatran, with stable and reproducible pharmacokinetic properties. No clinically significant interactions with food or cytochrome P450–metabolized drugs have been reported for ximelagatran, and the drug requires no monitoring (7).

INDICATIONS

Ximelagatran is undergoing evaluation for use in the prevention of stroke and other thromboembolic complications associated with atrial fibrillation, the prevention of venous thromboembolism (VTE) in patients undergoing knee replacement surgery, and the long-term secondary treatment of an episode of acute VTE (3).

PHARMACOLOGY

Ximelagatran is a prodrug that is rapidly converted after oral administration to the active compound melagatran. Melagatran is able to inhibit thrombin activity directly and quickly. The melagatran molecule binds to the arginine side pocket of thrombin, inactivating the thrombin. Melagatran can also inhibit thrombin generation. Both activated partial thromboplastin time and prothrombin time are increased with melagatran therapy and appear to correlate with the plasma concentration of melagatran (1, 2, 4, 5, 7).

PHARMACOKINETICS

The pharmacokinetics of ximelagatran are predictable and stable, independent of age, body weight, ethnic origin, or smoking preference (1, 2, 4, 5, 7). Ximelagatran has been evaluated in patients with deep vein thrombosis/pulmonary embolism, nonvalvular atrial fibrillation, and history of myocardial infarction. The pharmacokinetics are similar among these populations.

Absorption

Following oral administration of ximelagatran, oral bioavailability (measured as melagatran) is 18% to 25%. Peak melagatran levels after a ximelagatran dose of 48 mg twice daily are achieved within approximately 2 hours. Ximelagatran is 170 times more lipophilic than melagatran and remains uncharged when exposed to intestinal pH. Melagatran concentrations are proportional to the ximelagatran dose. Food has no significant effect on ximelagatran absorption.

Distribution

The volume of distribution of oral ximelagatran correlates with body weight and is larger than that of melagatran. Parenterally administered melagatran has a small volume of distribution of 0.22 L/kg. Plasma and serum protein binding is 0% to 15% for melagatran.

Metabolism/elimination

Ximelagatran is rapidly and extensively converted to melagatran in the liver and other tissues. This conversion is achieved by ester hydrolysis and reduction via two intermediate metabolites, hydroxymelagatran and ethylmelagatran. The predominant compound in plasma is the active drug, melagatran. The elimination half-life of melagatran after an oral dose of ximelagatran is 2.5 to 4.3 hours.

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Table 1. Summary of clinical trials of ximelagatran for thrombosis prevention in orthopaedic surgery

Author	Eriksson et al (8) (METHRO II)	Eriksson et al (9) (METHRO III)	Francis et al (6) (EXULT A study group)	Colwell et al (10)
Population	Adult patients (18–85 y) weighing 50–110 kg, post-TKR or -THR	Adult patients (≥18 y) weighing ≥40 kg, post-TKR or -THR	Adult patients weighing 40–136 kg, post-TKR	Adult patients (≥18 y) weighing ≥40–125 kg, post-TKR
Type of trial	Randomized, multicenter, double blind, double dummy, dose response	Randomized, multicenter, double blind, double dummy, parallel group	Randomized, multicenter, double blind	Randomized, multicenter, double dummy, parallel group
Duration of treatment	7–10 d after surgery	8–11 d after surgery	7–12 d after surgery	6–12 d after surgery
Number of subjects	1876	2788	2285—safety analysis 1851—efficacy analysis	1838
Treatment groups	—Dalteparin 5000 IU SQ daily —Melagatran SQ BID, followed by ximelagatran PO BID, 1 of 4 regimens: 1 mg/8 mg; 1.5 mg/12 mg; 2.25 mg/18 mg; 3 mg/24 mg. Melagatran SQ given immediately before surgery, 7–11 h after surgery, and continued for 1–3 d in most cases	—Enoxaparin 40 mg SQ daily, 12 h before surgery —Melagatran 3 mg SQ 4–12 h after surgery, followed by ximelagatran 24 mg PO BID	—Warfarin dose adjusted to INR 1.8–3 QPM —Ximelagatran 24 mg or 36 mg BID	—Enoxaparin 30 mg SQ BID, open label —Ximelagatran 8 mg, 12 mg, 18 mg, 24 mg PO BID, double blinded
Results—efficacy	—2/3 THR, 1/3 TKR —Evaluable venograms in 79% —Dose-dependent ↓ in frequency of VTE with ↑ doses of SQ melagatran and PO ximelagatran ($P < 0.0001$) —Frequency of VTE: 15.1% high-dose melagatran/ximelagatran, 28.2% dalteparin ($P < 0.0001$) —Frequency of proximal DVT, PE, or both: 2.5% high-dose melagatran/ximelagatran, 6.5% dalteparin ($P = 0.03$)	—THR 69% each group, TKR 31% each group —Frequency of VTE*: 31% melagatran/ximelagatran (95% CI: 28.3%–33.7%), 27.3% enoxaparin (95% CI: 24.6%–29.9%) ($P = 0.053$) —Difference in risk of total VTE statistically significant ($P = 0.004$) —Frequency of major VTE: 5.7% melagatran/ximelagatran (95% CI: 4.3–7.1%), 6.2% enoxaparin (95% CI: 4.7%–7.7%)	—Total VTE and death from all causes: 20.3% ximelagatran 36 mg ($P = 0.003$), 24.9% ximelagatran 24 mg ($P = 0.28$), 27.6% warfarin —Proximal VTE or death: 2.5% ximelagatran 24 mg ($P = 0.3$), 2.7% ximelagatran 36 mg ($P = 0.17$), 4.1% warfarin	—Total VTE: 16% ximelagatran, 23% enoxaparin —Proximal DVT or PE: 3% both groups —Per-protocol analysis: total VTE, 15% ximelagatran, 21% enoxaparin
Results—safety	—Severe bleeding, THR: 5.5% high-dose melagatran/ximelagatran, 2.3% dalteparin ($P = 0.002$) —Severe bleeding, TKR: 3.2% high-dose melagatran/ximelagatran, 2.4% dalteparin ($P = 0.002$) —Severe bleeding, total: 5% high-dose melagatran/ximelagatran, 2.4% dalteparin ($P < 0.0001$) —No significant difference in total frequency of adverse events between dalteparin and ximelagatran groups —ALT >3× ULN: 3.8% ximelagatran, 10.8% dalteparin (at follow-up, 4–6 wk, no difference between groups)	—Excessive bleeding: 1.4% ximelagatran (95% CI: 0.9%–2.2%), 1.7% enoxaparin (95% CI: 1.1%–2.5%) —Transfusion requirements and blood losses comparable in both groups	—Major bleeding: 0.8% ximelagatran 24 mg, 0.8% ximelagatran 36 mg, 0.7% warfarin —Any bleeding: 4.8% ximelagatran 24 mg, 5.3% ximelagatran 36 mg, 4.5% warfarin —ALT >3× ULN at venography: 5/757 (0.66%) ximelagatran 24 mg,† 8/769 (1%) ximelagatran 36 mg, 15/759 (1.98%) warfarin —ALT >3× ULN at 4–6 wk follow-up: 1/757 ximelagatran 24 mg, 5/769 (0.65%) ximelagatran 36 mg, 0/759 warfarin —Wound bleeding and appearance of wound revealed no significant differences	No significant differences between groups
Comments	—Design based on previous dose-ranging study (METHRO I) —Previous studies with dalteparin for preventing VTE reported lower rates	—Enoxaparin dose used is not recommended dose for prophylaxis of VTE after TKR (correct dose: 30 mg every 12 h)	Superiority of ximelagatran 36 mg proven only for reduction in rate of asymptomatic DVT; all other endpoints shown as equal efficacy	—No results statistically significant —Ximelagatran 8-mg arm discontinued after results from METHRO I showed it inferior to dalteparin; these patients added to remaining groups

*This difference was entirely accounted for by a higher frequency of distal DVT with ximelagatran vs enoxaparin in THR.

†Two patients in the ximelagatran 24 mg group had a baseline ALT ≥3× ULN.

TKR indicates total knee replacement; THR, total hip replacement; DVT, deep vein thrombosis; PE, pulmonary embolism; IU, International Unit; SQ, subcutaneous; BID, twice a day; PO, orally; QPM, every evening; INR, international normalized ratio; VTE, venous thromboembolism; CI, confidence interval; ALT, alanine aminotransferase; ULN, upper limit of normal.

Neither ximelagatran nor melagatran is metabolized by cytochrome P450 enzymes. The pharmacokinetics of melagatran following ximelagatran administration are not altered in patients with mild to moderate hepatic impairment.

Fourteen percent of melagatran is excreted through the urine after administration of oral ximelagatran. Clearance is correlated with creatinine clearance. In patients with severe renal impairment, melagatran clearance is reduced and half-life is approximately doubled.

CLINICAL TRIALS

Clinical trials of ximelagatran have been conducted for a variety of different patient populations. Because some of the data remain unpublished and/or were presented at scientific meetings, the following information may be incomplete.

Thrombosis prevention after orthopaedic surgery

Four comparative primary prevention trials have been conducted with ximelagatran in patients undergoing orthopaedic surgery. A summary of the trials is presented in *Table 1*.

Table 2. Summary of clinical trials of ximelagatran for stroke prevention in patients with atrial fibrillation

Author	Petersen et al (12) (SPORTIF II)	Halperin et al (13, 14) (SPORTIF III)	Halperin et al (14, 15) (SPORTIF V)
Population	Adults ≥18 y with history of chronic or persistent NVAF verified by at least 2 ECGs within previous year and at least 1 additional RF for stroke	Adults ≥18 y with history of persistent or paroxysmal NVAF verified by at least 2 ECGs (1 within 2 wk of randomization) and at least 1 additional RF for stroke	Same as SPORTIF III
Type of trial	Randomized, multicenter, parallel group, dose guiding	Randomized, multicenter, open label, parallel group	Randomized, multicenter, double blind, parallel group
Duration	12 wk	Minimum per-patient exposure of 12 mo, ≥4000 patient-years of follow up, and at least 80 primary events (mean duration, 17.4 mo)	Minimum per-patient exposure of 12 mo and maximum 24 mo, ≥4000 patient-years of follow-up, and ≥80 primary events (mean duration, 20 mo)
Number of subjects	254	3410	3922
Treatment groups	—Warfarin dose adjusted to INR 2–3, open label —Double-blind ximelagatran 20, 40, or 60 mg BID	—Warfarin dose adjusted to INR 2–3 —Ximelagatran 36 mg BID	—Warfarin dose-adjusted to INR 2–3 —Ximelagatran 36 mg BID
Results—efficacy	—1 TIA/1 ischemic stroke ximelagatran 60 mg and 2 TIAs warfarin —All doses of ximelagatran well tolerated	—Primary event: 1.6%/y ximelagatran, 2.3%/y warfarin ($P = 0.1$) —Primary event or death: 4.2% ximelagatran, 5.1% warfarin ($P = 0.1538$)	Primary event: 1.6%/y ximelagatran, 1.2%/y warfarin ($P = 0.13$, absolute difference 0.45%)
Results—safety	—No fatal bleeds —91% (231/254) had no bleeding on ximelagatran —Major bleeds: 0 ximelagatran, 1 warfarin —Minor bleeding: 4/66 20 mg, 5/62 40 mg, 7/59 60 mg ximelagatran; 6/67 warfarin —ALT >3× ULN after 4–8 wk: 4.3% (8/254) ximelagatran (5/8 resolved with continued treatment) —ALT elevations did not seem to be dose related	—Major bleeding: 1.3% ximelagatran, 1.8% warfarin ($P = 0.2281$) —Major or minor bleeding: 25.8% ximelagatran, 29.8% warfarin ($P = 0.0065$) —ALT >3× ULN: 6% ximelagatran, 1% placebo ($P < 0.0001$) —ALT elevations took place 2–6 mo and returned to baseline spontaneously or after treatment cessation	—Major or minor bleeding: 37% ximelagatran, 47% warfarin ($P < 0.0001$) —ALT >3× ULN: 6% ximelagatran, 0.8% placebo —ALT elevations took place 2–6 mo
Comments	—Exclusion criteria: stroke and/or embolism within 2 y and any heart valve patients —Compliance was 100%, 96%, 98% for 20-, 40-, 60-mg ximelagatran groups, respectively —Optimal INR values (2–3) for warfarin: 34% initially; 57% after 12 wk —Patient experiencing stroke had 5 RF in addition to NVAF	—Ximelagatran compliance 94% —INR values in goal range (2–3) 66%; in range of 1.8–3.2, 81%	Final results of trial pending publication

NVAF indicates nonvalvular atrial fibrillation; ECG, electrocardiogram; RF, risk factor; INR, international normalized ratio; BID, twice a day; TIA, transient ischemic attack; ALT, alanine aminotransferase; ULN, upper limit of normal.

Long-term secondary prevention of VTE

Long-term prophylaxis after standard treatment of an acute VTE is predicted to be the major use for ximelagatran. The purpose of the THRIVE III study was to assess the efficacy and safety of ximelagatran 24 mg twice daily compared with placebo for 18 months in patients with confirmed VTE. All 1233 participants randomized in the study had completed 6 months of anticoagulation therapy before enrollment. Ximelagatran significantly lowered the rate of recurrence of thromboembolism when compared with placebo: a confirmed thromboembolism occurred in 12 of 617 ximelagatran participants and 71 of 616 placebo participants ($P < 0.001$). Investigators estimated the cumulative risk of an event during 18 months of treatment to be 2.8% with ximelagatran and 12.6% with placebo ($P < 0.001$). There was no difference in major bleeding events between the groups (1.1% vs 1.3%; 95% confidence interval, 0.35–3.8). The 18-month cumulative risk for a major or minor bleeding event was estimated to be 23.9% and 21.0% for ximelagatran and placebo, respectively ($P = 0.17$). The incidence of an elevation in the alanine aminotransferase level to >3 times the upper limit of normal was statistically significant between the two groups (6% ximelagatran group, 1% placebo group, $P < 0.001$). The estimated cumulative risk of such an elevation at 18 months was 6.4% in the ximelagatran group and 1.2% in the placebo group ($P < 0.001$). However, it is important to note that the enzyme levels were resolved in a similar time course whether or not the drug was discontinued, and all elevations were asymptomatic (11).

Stroke prevention in patients with atrial fibrillation

Four SPORTIF (Stroke Prevention by Oral Thrombin Inhibitor in atrial Fibrillation) trials have been completed or are under way. SPORTIF II is a dose-guiding, tolerability, and safety study. SPORTIF III is a noninferiority, open-label trial. SPORTIF IV is an extension of the SPORTIF II trial, and SPORTIF V is a noninferiority, double-blinded trial. SPORTIF V results have been presented at a scientific meeting but have not yet been published. A summary of trials II, III, and V is presented in *Table 2*.

CONTRAINDICATIONS

Ximelagatran is contraindicated in patients with active severe bleeding. Precautions should be taken in patients at risk of bleeding, patients who have renal dysfunction, patients who are or may be pregnant, and patients who are breastfeeding (7). As noted above, melagatran clearance is reduced and half-life is approximately doubled in patients who have severe renal impairment (1, 2, 4, 5, 7). This is a major concern for a drug that is not being monitored. Again, caution should be exercised in this patient population due to an increased risk of bleeding.

Table 3. Treatment-related adverse events reported in ximelagatran-treated patients

Adverse event	Ximelagatran 36 mg	Warfarin	P value
Bleeding episode	25.8%	29.8%	0.0065
Severe bleeding	1.3%	1.8%	0.2281
Elevated ALT/AST >ULN	6%	1%	<0.0001

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

ADVERSE EFFECTS

Frequently reported adverse events among patients treated with ximelagatran in the clinical trials were excess bleeding and elevated alanine aminotransferase (13, 14) *(Table 3)*. Unlike other anticoagulants, ximelagatran has no reversal agent for a bleeding event. However, it is important to note that ximelagatran's half-life, between 2.5 and 4.3 hours, means that the drug is completely eliminated in a maximum of 21.5 hours.

DOSING AND ADMINISTRATION

Ximelagatran is dosed twice daily (7). In patients with chronic nonvalvular atrial fibrillation, oral ximelagatran 36 mg twice daily has been shown to be effective. For VTE prophylaxis, two approaches to dosing ximelagatran have been used: monotherapy and combination therapy. A daily dose of 24 mg and 36 mg has been studied in patients undergoing knee arthroplasty. The first dose is given on the morning after surgery or at least 12 hours after surgery, and treatment is continued for 7 to 12 days. In patients undergoing total knee or hip replacement surgery, the most effective therapy has been a single dose of subcutaneous melagatran 2 mg just before surgery (knife-to-skin) followed by melagatran 3 mg subcutaneously after surgery and then oral ximelagatran 24 mg twice daily for a total treatment duration of 8 to 11 days.

Dosing in renal insufficiency

The elimination half-life of melagatran is doubled in renal failure. In moderate to severe renal dysfunction, a longer dose interval or a downward dose adjustment (up to 50%) is appropriate.

Dosing in hepatic insufficiency

Ximelagatran has not been studied in severe liver disease. On the basis of pharmacokinetic data, no dose adjustment appears to be required in mild to moderate hepatic dysfunction.

Dosing in elderly patients

Data suggest that dosage adjustment of oral ximelagatran is unwarranted in older patients without renal impairment.

Pregnancy/lactation

No adequate and well-controlled studies in pregnant women have been published.

DRUG INTERACTIONS

Oral ximelagatran is not expected to alter the metabolism of drugs metabolized by cytochrome P450 isozymes, nor do melagatran pharmacokinetics appear to be altered by substrates of these isozymes. Melagatran pharmacokinetics are also not expected to be affected by inhibitors of these isozymes (1, 2, 4, 5, 7).

ECONOMIC ISSUES

Cost data are unavailable for ximelagatran while it is undergoing FDA approval. Ximelagatran's initial cost will likely be much greater than warfarin, which costs a few cents per day. However, decreased laboratory costs (e.g., no international normalized ratio [INR] checks) will also need to be factored into a cost analysis.

SUMMARY AND CRITICAL ISSUES

Ximelagatran, a new oral direct thrombin inhibitor, has been shown in several clinical trials to be at least as effective as warfarin in prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation and in VTE prophylaxis after knee replacement surgery. Ximelagatran was also compared with dalteparin and enoxaparin in the METHRO trials and was shown to be as effective (8, 9). However, it is important to note that in the METHRO trials shown here, subcutaneous melagatran was used initially and then participants were switched to oral ximelagatran. This seems unnecessary if the peak concentration for the oral direct thrombin inhibitor, ximelagatran, is reached within approximately 2 hours of administration. When compared with warfarin for the prevention of a VTE after total knee replacement, ximelagatran 36 mg twice a day was superior, although this benefit was due to a reduction in the rate of asymptomatic deep vein thrombosis. The ability to use a twice-daily fixed dose regimen without need for INR monitoring makes ximelagatran an attractive replacement for warfarin. In addition, the lack of drug interactions and dietary constraints with ximelagatran further simplifies its use. Liver function test abnormalities were one of the main side effects noted across all studies, and these abnormalities are currently under study. No studies have been published in patients with prosthetic valves or severe renal insufficiency or patients who are pregnant.

Ximelagatran was approved in France in December 2003 for preventing stroke in atrial fibrillation and for primary/secondary prevention of VTE in orthopaedic surgery. It was approved in the European Union in May 2004 for the latter indication. Phase IV data from these countries may provide further insight into the incidence and severity of elevated liver function tests with ximelagatran (16). As of September 13, 2004, ximelagatran was deemed not approvable by the FDA Cardiovascular and Renal Drugs Advisory Committee. Collection of further data to support the approval of this potentially hepatotoxic oral direct thrombin inhibitor is recommended (17).

In summary, clinical data support the use of ximelagatran in the prevention of stroke in patients with atrial fibrillation and in the prevention of VTE in patients undergoing orthopaedic surgery. It may be considered equivalent to existing therapies. Further safety data, especially in patients with active liver problems, are needed. At this time, monitoring for liver function test abnormalities after initiation of therapy should be recommended.

1. Gustafsson D, Elg M. The pharmacodynamics and pharmacokinetics of the oral direct thrombin inhibitor ximelagatran and its active metabolite melagatran: a mini-review. *Thromb Res* 2003;109(Suppl 1):S9–S15.

2. Eriksson UG, Bredberg U, Gislen K, Johansson LC, Frison L, Ahnoff M, Gustafsson D. Pharmacokinetics and pharmacodynamics of ximelagatran, a novel oral direct thrombin inhibitor, in young healthy male subjects. *Eur J Clin Pharmacol* 2003;59:35–43.
3. Food and Drug Administration. Cardiovascular and Renal Drugs Advisory Committee; notice of meeting. *Federal Register* 2004(August 10); 69(153): 48509–48510. Available at http://www.fda.gov/OHRMS/DOCKETS/98fr/04-18166.htm; accessed October 13, 2004.
4. Wahlander K, Lapidus L, Olasson C, Thuresson A, Eriksson U, Larson G, Eriksson H. Pharmacokinetics, pharmacodynamics and clinical effects of the oral direct thrombin inhibitor ximelagatran in acute treatment of patients with pulmonary embolism and deep vein thrombosis. *Thromb Res* 2002;107: 93–99.
5. Gustafsson D, Nystrom J, Carlsson S, Bredberg U, Eriksson U, Gyzander E, Elg M, Antonsson T, Hoffmann K, Ungell A, Sorensen H, Nagard S, Abrahamsson A, Bylund R. The direct thrombin inhibitor melagatran and its oral prodrug H 376/95: intestinal absorption properties, biochemical and pharmacodynamic effects. *Thromb Res* 2001;101:171–181.
6. Francis CW, Berkowitz SD, Comp PC, Lieberman JR, Ginsberg JS, Paiement G, Peters GR, Roth AW, McElhattan J, Colwell CW Jr; EXULT A Study Group. Comparison of ximelagatran with warfarin for the prevention of venous thromboembolism after total knee replacement. *N Engl J Med* 2003;349:1703–1712.
7. Hutchison TA, Shahan DR, eds. *DRUGDEX® System*. Greenwood Village, CO: MICROMEDEX, Inc., edition expires 9/2004.
8. Eriksson BI, Bergqvist D, Kalebo P, Dahl OE, Lindbratt S, Bylock A, Frison L, Eriksson UG, Welin L, Gustafsson D; Melagatran for Thrombin Inhibition in Orthopaedic Surgery. Ximelagatran and melagatran compared with dalteparin for prevention of venous thromboembolism after total hip or knee replacement: the METHRO II randomised trial. *Lancet* 2002;360: 1441–1447.
9. Eriksson BI, Agnelli G, Cohen AT, Dahl OE, Mouret P, Rosencher N, Eskilson C, Nylander I, Frison L, Ogren M; METHRO III Study Group. Direct thrombin inhibitor melagatran followed by oral ximelagatran in comparison with enoxaparin for prevention of venous thromboembolism after total hip or knee replacement. *Thromb Haemost* 2003;89:288–296.
10. Colwell CW Jr, Berkowitz SD, Davidson BL, Lotke PA, Ginsberg JS, Lieberman JR, Neubauer J, McElhattan JL, Peters GR, Francis CW. Comparison of ximelagatran, an oral direct thrombin inhibitor, with enoxaparin for the prevention of venous thromboembolism following total hip replacement. A randomized, double-blind study. *J Thromb Haemost* 2003;1:2119–2130.
11. Schulman S, Wahlander K, Lundstrom T, Clason SB, Eriksson H; THRIVE III investigators. Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. *N Engl J Med* 2003;349: 1713–1721.
12. Petersen P, Grind M, Adler J; SPORTIF II investigators. Ximelagatran versus warfarin for stroke prevention in patients with nonvalvular atrial fibrillation. SPORTIF II: a dose-guiding, tolerability, and safety study. *J Am Coll Cardiol* 2003;41:1445–1451.
13. Olsson SB; executive steering committee on behalf of the SPORTIF III investigators. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. *Lancet* 2003;362: 1691–1698.
14. Halperin JL; executive steering committee, SPORTIF III and V study investigators. Ximelagatran compared with warfarin for prevention of thromboembolism in patients with nonvalvular atrial fibrillation: rationale, objectives, and design of a pair of clinical studies and baseline patient characteristics (SPORTIF III and V). *Am Heart J* 2003;146:431–438.
15. Early trial results from SPORTIF V. Presented at the Scientific Sessions of the American Heart Association, November 9–12, 2003. *First Report* 2003. Available at http://www.princetoncme.com/pdf/FirstReport_SportifV.pdf; accessed October 29, 2004.
16. AstraZeneca. Press releases. Available at http://www.astrazeneca.com/archivelist/2003.aspx; accessed October 13, 2004.
17. FDAAdvisoryCommittee.com. AstraZeneca Exanta liver toxicity outweighs benefit, cmte. says. Available at http://www.fdaadvisorycommittee.com/FDC/AdvisoryCommittee/Committees/Cardiovascular+and+Renal+Drugs/091004_Exanta/091004_ExantaR.htm; accessed October 13, 2004.